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FEATURE REVIEW

PANDAS: current status and directions for research

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The recognition of the five criteria for PANDAS (pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections) by Swedo *et al* established a homogenous subgroup of children with childhood onset obsessive–compulsive disorder (OCD) and/or tic disorders. The five clinical characteristics that define the PANDAS subgroup are the presence of OCD and/or tic disorder, prepubertal age of onset, abrupt onset and relapsing–remitting symptom course, association with neurological abnormalities during exacerbations (adventitious movements or motoric hyperactivity), and a temporal association between symptom exacerbations and a Group-A beta-hemolytic streptococcal (GAS) infection. These five criteria have been used for the purpose of systematic research on the phenomenology and unique therapies for the PANDAS subgroup as well as studies of the pathophysiology of post-streptococcal OCD and tic disorders. The etiology of OCD and tics in the PANDAS subgroup is unknown, but is theorized to occur as a result of post-streptococcal autoimmunity in a manner similar to that of Sydenham's chorea. The working hypothesis for the pathophysiology begins with a GAS infection in a susceptible host that incites the production of antibodies to GAS that crossreact with the cellular components of the basal ganglia, particularly in the caudate nucleus and putamen. The obsessions, compulsions, tics, and other neuropsychiatric symptoms seen in these children are postulated to arise from an interaction of these antibodies with neurons of the basal ganglia.
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Perseverative behaviors were first noted in patients diagnosed with Sydenham's chorea (SC) at the end of the 19th century.[1] SC is the well-recognized neuropsychiatric manifestation of rheumatic fever in which patients develop chorea along with other neuropsychiatric symptoms after a preceding Group-A beta-hemolytic streptococcal (GAS) infection.[2] The symptoms of perseverative behaviors or compulsions and intrusive thoughts or obsessions are diagnostic criteria for obsessive–compulsive disorder (OCD). Clinical reports noted an association between SC and OCD among children with rheumatic chorea, and adult psychiatric patients with a history of SC.[3–5] Research studies conducted at the National Institute of Mental Health reported the association of OCD in patients with SC and also found a subgroup of children who had OCD and/or tic disorders following a GAS infection without meeting the criteria for SC.[6–8] The subgroup is identified by the acronym, PANDAS, for pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections.[9] Several authors have questioned the validity of this designation and others have questioned the postulates of etiopathogenesis;[10,11] A pair of recent editorials summarizes this debate.[12,13] The recent literature has replicated the NIMH findings and is beginning to address the question of etiopathogenesis. We present a review of the published data and note where further information is required.

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SC and PANDAS

Clinical parallels between SC and the PANDAS subgroup suggest that the two disorders may have a shared etiopathogeneis.[14,15] The evidence for basal ganglia dysfunction in SC has been derived from volumetric MRI studies that demonstrated striatal enlargement,[16] post-mortem studies that found focal cellular infiltration and neuronal loss within the basal ganglia,[17,18] as well as clinical response to dopaminergic agents. Systematic research over the past two decades has demonstrated that OCD is associated with dysfunction in the basal ganglia and orbitofrontal cortex[19] (Figure 1). Structural and functional neuroimaging studies have demonstrated abnormalities of the basal ganglia structures and their related corticostriato-thalamocortical circuitry in the pathobiology of OCD.[20–24]

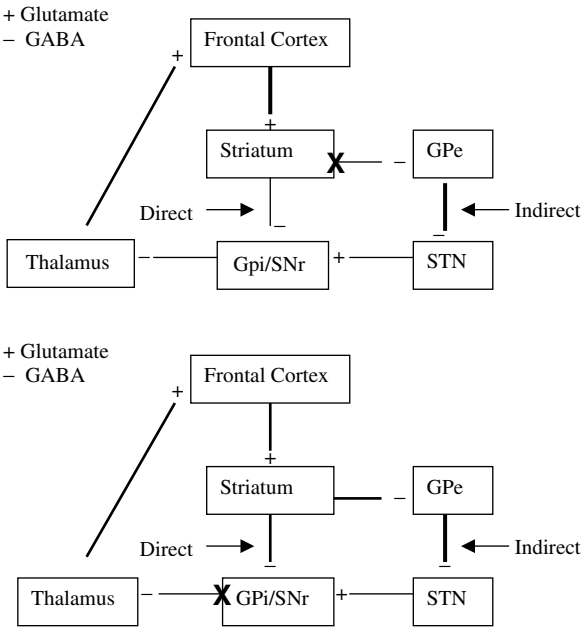

Figure 1 Models of possible areas of basal ganglia dysfunction in obsessive–compulsive disorder and tic disorders. In this model, the primary area of dysfunction is in the striatum, reducing its inhibition of the globus pallidus externa (GPe), which causes the GPe to increase its inhibition of the subthalamic nucleus (STN), thus reducing the STN's stimulation of the globus pallidus interna/substantia nigra (GPi/SNr). This causes a reduction in GPi/SNr inhibition of the thalamus, which then can increase its stimulation of the frontal cortex. In this alternative construct, the GPi is the primary site of pathology. Without the GPi's inhibition, the thalamus increases its stimulation of the frontal cortex, which could produce symptoms directly, or through increased stimulation of the striatum.

Indirect evidence for basal ganglia involvement in OCD is provided by the efficacy of psychosurgical lesions that disconnect the basal ganglia from the frontal cortex, particularly capsulotomy[25] and cingulotomy.[26] In capsulotomy, lesions that are made in the limb of the internal capsule are thought to primarily interrupt the orbito-frontal and subgenual anterior cingulum cortex and thalamic connections. Edema or other secondary effects might also affect the frontal-striatal circuits.[27] In order to perform a cingulotomy, the anterior portion of the cingulate gyrus is lesioned, interrupting tracks between the cingulate gyrus and the frontal lobes and destroying all of the efferent projections of the anterior cingulate cortex. Both procedures result in significant reduction of obsessions and compulsions. The success of psychosurgery is not conclusive evidence of a basal ganglia defect in OCD, as the lesions could be anywhere 'upstream' from the site of the lesion, but it does focus interest on frontal-striatal tracts.[28]

There is significant symptom overlap in patients with SC and childhood onset OCD.[3,6,8] For nearly in three-quarters of SC patients, the neuropsychiatric symptoms include obsessions and compulsions identical to those seen in childhood-onset OCD: contamination concerns, worries about harm coming to self or others, violent images, and checking, washing and arranging rituals.[6,7,14] These obsessive–compulsive symptoms are reported to begin 2–4 weeks before the onset of the adventitious movements, leading to speculation that OCD might occur as a sequela of streptococcal infections, even in the absence of frank chorea.[14] This postulate was confirmed by prospective observations of a large cohort of children and adolescents with OCD.[29] A subgroup of pediatric patients with OCD was observed to have an unusual clinical course characterized by abrupt symptom onset and a relapsing–remitting pattern of severity; often, the symptom relapses followed streptococcal throat infections or bouts of scarlet fever.[8]

Motor and vocal tics, including Tourette syndrome, occur frequently in association with OCD. The relationship between tics and OCD is complex, as motor tics often have a behavioral component suggestive of compulsive rituals, while the compulsions seen in OCD may lack accompanying obsessive thoughts, making them look like tics if the rituals are simple, repetitive behaviors such as touching or tapping. The overlap between tics and OCD is most apparent in pediatric patient populations, where up to two-thirds of children with OCD are observed to have comorbid tics[30] and 20–80% of children with Tourette syndrome report obsessive–compulsive symptoms.[31] It is unknown just how the pattern and severity of obsessive–compulsive symptoms differ between patients with Tourette syndrome and those with primary OCD, but preliminary impressions suggest that the compulsions associated with Tourette syndrome are more likely to involve symmetry, rubbing, touching, staring or blinking rituals, than washing and cleaning.[31] There have also been studies documenting the onset of tic disorders after infection with GAS. For example, exposure to streptococcal antigens correlated with the onset of tics in an Italian pediatric population.[32] An association between a community outbreak of GABHS infections and a 10-fold rise in the number of children presenting with a new onset of tics also has been documented.[33]

Pathogenesis of SC

Although the exact pathogenesis has not yet been established, GAS is known to be the inciting agent in the development of rheumatic fever and SC (Figure 2).[34] For rheumatic fever, the etiologic role of GAS infections was demonstrated indirectly, through three lines of research: (1) epidemiologic investigations, which demonstrated a close temporal relationship between scarlet fever epidemics and subsequent outbreaks of rheumatic fever; (2) the prevention of rheumatic fever recrudescences by penicillin prophylaxis, and (3) demonstration of declining rates of rheumatic fever following the widespread application

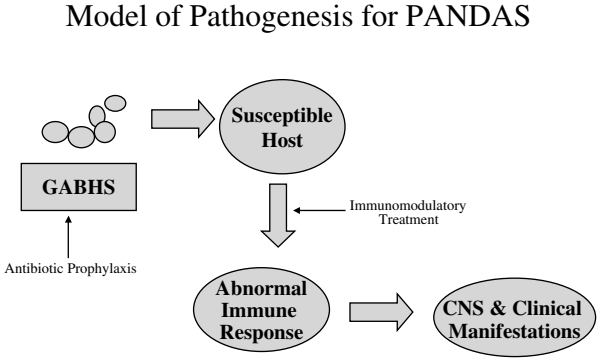

Figure 2 Model of etiopathogenesis for SC and the PANDAS subgroup.

of antibiotic treatment for GAS pharyngitis.[35] The relationship between GAS infections and rheumatic fever was established by demonstrating a temporal relationship between epidemics of streptococcal infections (scarlet fever and streptococcal pharyngitis), and subsequent outbreaks of rheumatic fever.[36,37] These findings were extended by demonstrating that each time the incidence of scarlet fever increased, it was followed 3 weeks later by a rise in the rate of rheumatic fever cases.[38] Although epidemiological studies are not usually sufficient to establish causality, the clarity of the relationship in these investigations has been accepted as evidence that GAS infections are the etiologic trigger in rheumatic fever.[39]

The production of antibodies to streptococcal antigens associated with the M-protein of GAS have been shown to crossreact with epitopes on neuronal tissue. This has been proposed as a possible etiology for the central nervous system sequlae of SC.[40,41] Husby *et al* were the first to describe crossreactive antibodies in SC. These antineuronal antibodies were raised against epitopes on the GAS bacteria, but also crossreacted with cells of the caudate nucleus and subthalamus. It was the crossreactivity with GAS which distinguished the antibodies found in the SC patients from antineuronal antibodies found in patients with lupus erythematosus and other neurologic disorders.[40] It has also been purposed that the pathogenesis of chorea results from immune complex disease produced by nondestructive antistreptococcal antibodies that localize to the basal ganglia and striatial areas of the brain.[9,40,42]

Recent investigations have confirmed these findings and new evidence implicates antibody-mediated neuronal cell signaling as a possible pathogenesis for the neuropsychiatric symptoms seen in patients with SC. Semiquantitative assays (ELISA and Western immunoblotting) were developed to detect anti-basal ganglia antibodies that crossreacted with GAS and compared them to standard immunoflurocence (IF) methods. The standard IF method has been proposed as a possible explanation for the variable findings of anti-basal ganglia antibodies in SC since the results rely on a subjective determination of positivity unlike ELISA or Western immunoblotting. Assays were performed on serum samples from 36 subjects with SC (20 with acute symptoms and 16 with chronic symptoms lasting longer than 2 years), 16 subjects with rheumatic fever without chorea, and 11 healthy volunteers to detect anti-basal ganglia antibodies. Three distinct basal ganglia antigens were isolated: a 40, a 45, and a 60 kDa protein. Both Western immunoblotting and IF had a sensitivity of 100% and specificity of 93% in the acute SC which dropped significantly in the chronic SC.[43] Samples of cerebrospinal fluid from patients with SC was found to contain anti-basal ganglia antibody-specific IgG which bound to the same antigens (40, 45, and 60 kDa basal ganglia proteins) that the serum sample recognized.[44]

A recent study suggests that antibodies against GAS isolated in acute SC stimulate neurons from the basal ganglia through specific induction of a calcium/calmodulin-dependent protein (CaM) kinase within the neuron. This specific CaM kinase was stimulated above the basal rate by both the isolated antibody as well as by acute SC serum. It was not found to be stimulated above the basal rate by convalescent SC or by normal healthy sera. Cerebral spinal fluid from acute SC was also found to induce the specific CaM kinease.[45] This evidence for biologic activity through neuronal signal transduction identifies a possible mechanistic role for antineuronal antibodies in the pathogenesis of SC.

Pathogenesis of PANDAS

The role of the immune system in the etiology of PANDAS has not been established, but current research suggests that symptoms result from a combination of local, regional, and systemic abnormalities.[46–49] There is also evidence for a genetic predisposition as the rates of tic disorders and OCD in first-degree relatives of children in the PANDAS subgroup are higher than those in the general population, and similar to those previously reported for tic disorders and OCD.[50] Several groups have reported the presence of antineuronal antibodies among patients with childhood-onset OCD and/or tic disorders.[51–55] Preliminary animal studies suggest these antineuronal antibodies may play an etiologic role in these neuropsychiatric disorders,[56–58] although there have been negative reports from investigators who were not able to induce behavioral changes through an infusion.[59] The striking effectiveness of immunomodulatory therapies, such as therapeutic plasma exchange and intravenous immunoglobulin (IVIG) in the PANDAS subgroup, suggests that there is systemic involvement, at least in severely affected individuals.61 Magnetic resonance imaging scans reveal enlargements of the caudate, putamen, and globus pallidus, which points to regional inflammatory changes,[60,61] while local autoimmune reactions are suggested by the presence of serum antibodies

which cross-react with neurons of the caudate, putamen, and globus pallidus.[51,62]

The pathobiology of the neuropsychiatric symptoms in the PANDAS subgroup is postulated to be similar to that of SC. The etiopathogenesis is hypothesized to occur when GAS bacteria infect a susceptible host and induce an abnormal immune response. As shown in Figure 2, the proposed model not only provides a framework for understanding the etiology of PANDAS but also for the development of novel intervention and prevention strategies. The associative strategy employed for rheumatic fever can be applied to the question of the relationship between GAS infections and OCD/tic symptoms in the PANDAS subgroup. One caveat in evaluating the relationship between streptococcal infections and neuropsychiatric symptoms is that the disorders are so common that co-occurrence can be a random coincidence, rather than a clinically significant finding. OCD occurs in 1–2% of school-age children, and transient motor tics in as many as 10–25% of early elementary students.[63,64] Further, during regional streptococcal epidemics, the majority of children will be infected at least once during the outbreak.[65] Thus, a single positive throat culture or elevated antistreptococcal antibody titer is not sufficient to determine that a child's neuropsychiatric symptoms are associated with streptococcal infections.[66,67] The determination that a child fits the PANDAS profile is made through prospective evaluation and documentation of the presence of streptococcal infections in conjunction with at least two episodes of neuropsychiatric symptoms, as well as demonstrating a negative throat culture or stable titers during times of neuropsychiatric symptom remission.[68] Although the first episode of OCD or tics in a child can be very suggestive of PANDAS if it reaches clinical impairment within 24–48 h, it is associated with a new onset of enuresis, separation anxiety or hyperactive symptoms, and is preceded by a GAS infection. A child who has multiple symptom exacerbations without evidence of streptococcal infection would not be considered as part of the PANDAS subgroup, nor would a child who has numerous streptococcal infections without subsequent symptom exacerbations.

The reduction of rheumatic fever (RF) recurrences by antibiotic prophylaxis against GAS infections was a key factor in determining that GAS played an etiologic role in RF. This was particularly true for SC, in which evidence of an inciting GAS infection was often unobtainable.[35] Antibiotic prophylaxis not only prevented recrudescences but also improved the long-term prognosis of RF sufferers, by preventing additional scarring of the cardiac valves.[69] The same goal may apply to the obsessive–compulsive symptoms associated with SC. A recent report from Sao Paulo, Brazil demonstrated that the frequency and severity of obsessive–compulsive symptoms increased with repeated bouts of SC.[70] During the initial choreic episode, approximately 65% of the patients had obsessive–compulsive symptoms, which were reported to be 'mild' and nonimpairing. If the child had two or more recrudescences, the risk of OCD increased to 100%, and all children reported clinically significant symptomatology.[70] It is also interesting to note that children with rheumatic fever without SC were found to have an increase in obsessive–compulsive symptoms over controls.[71]

In order to determine whether or not antibiotic prophylaxis against GAS infections would be effective in reducing the number and severity of neuropsychiatric symptom exacerbations, a double-blind crossover comparison of penicillin and placebo was conducted for children in the PANDAS subgroup.[72] The hypothesis of the study was that penicillin prophylaxis would prevent GAS infections and therefore, post-streptococcal neuropsychiatric symptom exacerbations, resulting in an overall decrease in OCD/tics symptom severity during the penicillin phase (4 months), as compared with the placebo phase (4 months). However, oral penicillin administration failed to provide adequate prophylaxis against GAS, as evidenced by the fact that 14 of the 35 GAS infections occurred during the penicillin phase. Without significant between-phase differences in infection rates, it was not surprising that ratings of OCD and tics symptom severity were not significantly improved during the penicillin phase. Of note, however, among those children for whom penicillin was an effective prophylactic agent, overall behavior was improved, with the penicillin phase ranked as superior to placebo by 75% of the parents who could discern a between-phase difference.[72]

The results of the pilot investigation were sufficiently promising to justify a trial of a potentially more effective prophylactic agent, azithromycin (its once a week dosing schedule is associated with improved compliance) Preliminary results from the first 23 subjects to finish a 12-month, parallel-design double-blind trial of azithromycin and penicillin found the rate of GAS infections among the study participants was significantly less during the year of antibiotics administration (0.1 (SD 0.3) per year) than during the year prior to the study (2.2 (SD 1.2) per year; $P<0.01$), whether children were randomized to penicillin or azithromycin.[73] There were two subjects with a positive throat culture for GABHS (one from each antibiotic group), but no subjects had a significant rise in anti-streptococcal titers (antistreptolysin or anti-deoxyribonuclease B) during the study year. There were no significant differences in the number of streptococcal infections or number of neuropsychiatric exacerbations between the penicillin and azithromycin groups. These preliminary data suggest that both penicillin and azithromycin may be effective in preventing post-streptococcal neuropsychiatric exacerbations. A placebo-controlled investigation of the efficacy and effectiveness of antibiotics prophylaxis would be required prior to the extrapolation of these findings to all children in the PANDAS subgroup. Such studies are underway at the NIMH and elsewhere.

The most compelling evidence for a role for immunologic dysfunction in the PANDAS subgroup comes from results of a randomized, placebo-controlled trial of intravenous immunoglobulin (IVIG) and plasma exchange.[74] Both immunomodulatory therapies produced significant improvements in neuropsychiatric symptom severity. Placebo IVIG administration had no demonstrable effect on obsessive–compulsive symptoms at 1 month follow-up, while IVIG and plasma exchange treatments had produced mean symptom reductions of 45 and 58% (respectively). The 1-year follow-up revealed that 14 of 17 children (82%) continued to be 'much' or 'very much' improved from baseline.[74] The effectiveness of the immunomodulatory therapies suggests that circulating immune factors play a role in the pathophysiology of the symptoms, but no specific hypotheses can be formulated on the basis of the treatment response because of the broad spectrum of action of both IVIG and plasma exchange.

Recent investigations on the presence of antineuronal antibodies in tic disorders and childhood onset OCD have been promising. Western immunoblotting was utilized to examine serum samples from 100 unselected Tourette syndrome (TS) subjects (56 children mean age 13 years and 44 adults mean age 38 years), and found that 20% of the children and 27% of the adults with TS had anti-basal ganglia antibodies that were crossreactive with GAS. The most common basal ganglia antigen recognized by the antibodies was a 60 kDa protein that was similar to one isolated in patients with SC. Only 2–4% of the control groups (children with an uncomplicated GAS infection, children with other neurologic disorders, adults with other neurologic disease, and adult healthy controls) were found to have these antibodies.[62] Using similar methodologies, anti-basal ganglia antibodies crossreactive with GAS were demonstrated in 42% ($n = 21$) of children with childhood-onset OCD compared to 2–10% of the pediatric control groups: autoimmune disorders, other neurologic disorders, and uncomplicated GAS infection. (Dale, 2003 personal communication.) Neither the TS group nor the OCD group in these studies was selected with respect to fitting the criteria for PANDAS. It would be interesting to know which of the TS and OCD subjects did meet the PANDAS criteria and then compare them to the subjects who did not with respect to positive crossreactive anti-basal ganglia antibodies. Investigators are now finding antineuronal antibodies among the PANDAS subgroup that are specific to the basal ganglia as well.[75,76] Preliminary results suggest that an antineuronal antibody found in SC patients that stimulates neuronal transduction may also be present in a group of PANDAS subjects (Kirvan, 2003 personal communication).

Clinical features of the PANDAS subgroup

The clinical features of the first 50 children meeting criteria for the PANDAS subgroup were published and established the five criteria for inclusion in the subgroup.[66]

(1) The presence of a tic disorder and/or OCD.
(2) Prepubertal age at onset, usually between 3 and 12 years of age.
(3) Abrupt symptom onset and/or episodic course of symptom severity
(4) Temporal association between symptom exacerbations and streptococcal
(5) infections.
(6) Presence of neurological abnormalities during periods of symptom exacerbation.

Several unique characteristics of the PANDAS subgroup become apparent when the children are compared to unselected patients with childhood-onset OCD and tic disorders.[66,68,77–79] The average age at symptom onset in the PANDAS subgroup is nearly 3 years younger than that previously reported for childhood-onset OCD[29,80] and up to 2 years younger than the average age of onset for tic disorders.[31] Further, comparisons of the age and sex distribution of the PANDAS subgroup with that of other OCD patient groups suggests a bimodal distribution.[29,66] This is consistent with the postulate that the PANDAS subgroup is distinct from other patient groups; however, this cannot be confirmed without large-scale community-based investigations, or the demonstration of a unique etiopathogenesis for the PANDAS subgroup.

The clinical course of the PANDAS subgroup differs markedly from that of other OCD patients.[29,66] Symptom exacerbations in the PANDAS subgroup are sudden and severe, with parents describing the onset of symptoms as occurring 'overnight' or 'out of the blue.' The symptoms remain at peak severity for a period of several weeks or longer, and then gradually subside in severity, often remitting completely, with patients remaining asymptomatic until they are infected again with GAS. This relapsing–remitting course is in striking contrast to the gradual onset and persistent symptoms typically seen in childhood-onset OCD[29,81] and also differs substantially from the waxing and waning course of tic disorders.[31] Emotional lability, attentional difficulties, separation anxiety, and motoric hyperactivity frequently accompany the OCD/tics exacerbations in the PANDAS subgroup;[66] these clinical features are shared with SC. Enuresis and daytime urinary frequency are also common.[66,79] In addition, deteriorations in handwriting also have been noted during the symptom exacerbations in the PANDAS subgroup, and may prove useful as an objective means of tracking symptom severity.[67]

Although the etiology of the handwriting changes is not known, they appear to parallel the appearance of choreiform movements of the hands and fingers. The presence of choreiform movements during neuropsychiatric symptom exacerbations may prove to be one of the most reliable means of identifying children in the PANDAS subgroup.[15] These mild adventitious

movements can be elicited during structured neurological examinations, such as the PANESS (physical and neurological examination for soft signs),[82] and were found to be present in 25 of 26 children in the original cohort who were examined during an exacerbation.[66] The choreiform movements are thought to arise from dysfunction of the basal ganglia of the brain, particularly within the caudate nucleus and putamen. These structures are also implicated in OCD, where symptoms are postulated to result from dysfunction of the corticostriato-thalamocortical circuitry.[83] In SC, functional imaging studies provide evidence of basal ganglia dysfunction during acute chorea,[84,85] and volumetric abnormalities of the caudate, putamen, and globus pallidus were demonstrated in a cohort of 24 children with SC through the use of structural MRI scans.[16] A volumetric MRI study of 34 children in the PANDAS subgroup also revealed enlargements of the caudate, putamen, and globus pallidus.[61] In some patients, the size of the basal ganglia structures was found to normalize following successful immunomodulatory therapy with IVIG or plasma exchange.[60]

In summary, there is a growing body of evidence supporting an etiologic role for molecular mimicry in post-streptococcal neuropsychiatric symptoms (SC and PANDAS). Crossreactive antibodies recognizing both GAS cellular components and basal ganglia tissue have been observed. The cells recognized by the antibodies are localized to brain regions consistent with the clinical presentation of the disorders, and also, with earlier findings from pathological examinations in SC and neuroimaging investigations of SC, OCD and tic disorders. Recent reports of biological activity for these antibodies provide further support for the postulate that the antibodies play a role in the etiopathogenesis of both SC and the symptoms observed in the PANDAS subgroup. However, the mechanism by which these crossreactive antibodies produce neuropsychiatric symptoms remains to be elucidated. Future research should address questions of the regional specificity and cellular basis for the autoimmune aspects of this disorder, as well as clinical and epidemiological issues.

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